PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32716A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11034	International filing date *(day/month/year)* 06.10.2003	Priority date *(day/month/year)* 07.10.2002
International Patent Classification (IPC) or both national classification and IPC C07D223/24		
Applicant NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.04.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Seitner, I Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11034

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15 and 16 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 15 and 16 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	5-21
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	5-21
Industrial applicability (IA)	Yes:	Claims	1-14,17-21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15 a nd 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 00/76942 A (LE GUYADER FREDERIC ;MOHAR BARBARA (FR); SCHLAMA THIERRY (FR); WAG) 21 December 2000 (2000-12-21)

D2: MOHAR, BARBARA ET AL: "Highly enantioselective synthesis via dynamic kinetic resolution under transfer hydrogenation using Ru(.eta.6-arene)-N-perfluorosulfonyl-1,2-diamine catalysts: a first insight into the relationship of the ligand's pKa and the catalyst activity" CHEMICAL COMMUNICATIONS (CAMBRIDGE, UNITED KINGDOM) (2001), (24), 2572-2573, XP002270702

D3: TARAN F ET AL: "HIGH-THROUGHPUT SCREENING OF ENANTIOSELECTIVE CATALYSTS BY IMMUNOASSAY" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 41, no. 1, 4 January 2002 (2002-01-04), pages 124-127, XP001102322 ISSN: 0570-0833

D4: BENES J ET AL: "Anticonvulsant and Sodium Channel-Blocking Properties of Novel 10,11-Dihydro-5H-dibenz[b,f]azepine-5-carb oxamide Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 2582-2587, XP002206156 ISSN: 0022-2623

D5: HAACK K J ET AL: "The catalyst precursor, catalyst and intermediate in the RuII-promoted asymmetric hydrogen transfer between alcohols and ketones"

ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 36, no. 3, 1997, pages 285-288, XP002092423 ISSN: 0570-0833

D6: LISGARTEN, JOHN N. ET AL: "The structure of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]aze pine-5- carboxamide, an anticonvulsant drug molecule" ACTA CRYSTALLOGRAPHICA, SECTION C: CRYSTAL STRUCTURE COMMUNICATIONS (1989), C45(4), 656-8, XP008027747

V.1. Novelty:

The prior art does not disclose a process as described in present claim 1. Therefore, the subject-matter of **claims 1-4 is novel (Article 33(2) PCT).**

Document D1 discloses the ligand (1S,2S)-N-(3,5-bis (trifluorométhane) phénylsulfonyl) 1,2-diphényléthylènediamine (see page 12, lines 16-17, example 20) and the reduction of acetophenone using said ligand, forming a complex with $[RuCl_2(p\text{-cymene})]_2$ during the reaction (see example 24, tables 6 and 7).
D2 discloses the ligand (1S,2S)-N-(p-trifluorométhyl-phénylsulfonyl)-1,2-diphényléthylènediamine (see table 1, example 4b) and its Ru-complex with p-cymene.
D3 discloses also the (1S,2S)-N-(p-trifluorométhyl-phénylsulfonyl)-1,2-diphényléthylènediamine ligand (see scheme 1, ligand L4) forming a complex with $[RuCl_2(p\text{-cym})]_2$ (see M1).
The complexes described in D1-D3 fall within the scope of the general formulae (III'a) and (III'b) of claim 5.
Therefore, the subject-matter of **claim 5 is not novel** over the prior art **(Article 33(2) PCT).**

Claims 6-21 relates to crystal forms of both enantiomers of 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, their pharmaceutical use and compositions as well as the process for preparing them.
Document D4 discloses both enantiomers of 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide and D6 gives details on crystallographic data of 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide. Compounds are not necessarily novel and almost certainly not inventive, just because some physical property is different from the one disclosed in the prior art. In the present case it is not apparent, in what respect the

compounds of claims 6-9 should be distinct from the 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide of the prior art. Therefore, the subject matter of **claims 6-21 cannot be considered as novel over the prior art (Article 33(2) PCT).**

V.2. Inventive Step:

The document D4 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (see page 2585, paragraph 3 - page 2586, paragraph 2) the preparation of both enantiomers of 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamides by reducing the corresponding keto-compound via $NaBH_4$ and subsequent resolution into the enantiomers by means of fractional crystallization.

The subject-matter of claim 1 therefore differs from this known process in that the reduction of the keto group is enantioselective by using the reducing agents according to the general formulae (IIIa)-(VIB) of claim 1.

The problem to be solved by the present invention may therefore be regarded as the provision of a further process for the preparation of both enantiomers of 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamides.

From D5, the use of catalysts according to present agents (IIIa) and (IIIb) for enantioselective reduction of keto-groups is known. However, the compounds to be reduced in D5 is acetophenone and derivatives thereof. No incentive for the skilled person can be found in D5 to use the catalysts of D5 for the enantioselective reduction of dibenzo-azepine compounds.

Therefore, the subject-matter of **claims 1-4** relating to the process and the novel subject-matter of **claim 5** relating to the reducing agents (III'a) and (III'b) are considered as involving an **inventive step (Article 33(3) PCT).**

V.3. Industrial Applicability:

The present application relates to 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamides which are useful for the treatment of epilepsy and therefore the subject-matter of **claims 1-14 and 17-21 is industrially applicable (Article 33(4) PCT).**

For the assessment of the present claims 15 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.